

**REMARKS/ARGUMENTS**

Claims 1-28 are pending. Claims 20 and 25 have been amended to recite “greater than 1:1.” Claim 28 has been amended to recite “said inattentiveness in an ADHD human patient.”

**Objection to claim 28**

According to the Examiner, the claim 28 phrase “said inattentiveness later in the day” lacks antecedent basis. Claim 28 has been amended to recite “said inattentiveness in an ADHD human patient.” This phrase has antecedent basis. Accordingly, this rejection should be withdrawn.

**Objections to the specification**

The Examiner has maintained the objection based on the presence of a hyperlink in the specification. The Examiner has also objected to the amendment of “ADDERALL®” in the previous response. According to the Examiner, the as-filed specification recited “ADDERALL® XR.” These objections are obviated by the amendments to the specification.

**Rejection of claims 20 and 25 under 35 U.S.C. § 112, second paragraph**

The Examiner maintained the rejection of claims 20 and 25 under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph because he contends that the phrase “greater than about 1:1 or contains 1 isomer only” is indefinite. According to the Examiner, “greater than” indicates a ratio above 1:1, whereas “about” indicates that there is variation above or below the 1:1 ratio. This rejection is obviated by the amended claims 20 and 25, which recite “greater than 1:1.”

**Rejection of claims 1-28 under 35 U.S.C. § 103(a)**

Claims 1-28 have been rejected as obvious over (1) Patrick et al., Human Psychopharmacology 1997;12:527-546 (Patrick) in view of (2) Hartmann et al., Psychopharmacology 1976;50:171-175; (3) WO 02/039998 (Epstein); (4) Drug Facts and Comparisons 1996;1230-1233; and (5) Remington’s Pharmaceutical Sciences (Sixteenth edition, 1980) 1594-1602.

According to the Examiner:

(1) Patrick discloses that:

(a) dextroamphetamine and levoamphetamine mixed salts (ADDERALL) can be used for the treatment of ADHD;

(b) ADDERALL® is a combination of dextroamphetamine saccharate, dextroamphetamine sulfate, racemic amphetamine aspartate and racemic amphetamine sulfate; and

(c) “the total free base equivalence in, for example, a 10 mg tablet is 6.3 mg, of which 81% is dextroamphetamine and 19% is levoamphetamine.”

Further, according to the Examiner, Patrick discloses that ADDERALL® is composed primarily of dextroamphetamine and exhibits side effects similar to dextroamphetamine alone.

The Examiner acknowledges that Patrick does not disclose: (i) a pharmaceutical composition wherein the molar ratio of l-amphetamine to d-amphetamine released later in the day is higher than the ratio released earlier in the day; (ii) the use of such a composition to treat ADHD; (iii) the particularly claimed ratios; and (iv) single or separate dosage forms with the claimed release profile.

(2) Hartman discloses that “in general the amphetamines produce cortical arousal or activation and that they promote wakefulness in man at times of drowsiness or sleep deprivation” and the “dextro-isomer has usually been found to be more potent in these regards than the levo-isomer.”

(3) Epstein discloses that levoamphetamine is a more potent memory enhancer than dextroamphetamine and is not addictive.

(4) Drug Facts and Comparisons discloses the untoward effects of the d-isomer on sleep patterns.

(5) Remington discloses various methods to achieve “differing release profiles such as immediate, pulsed, controlled or sustained release.”

According to the Examiner: “[W]hile the l-isomer of amphetamine was known to have fewer peripheral sympathomimetic side effects than the d-isomer, it was known in the art that it did not have as great an effect on maintaining wakefulness as the d-isomer of amphetamine.” The Examiner states: “An ideal regimen for the treatment of attention-deficit hyperactivity disorder and

the inattentiveness that is associated with such a condition would balance an effective amount of stimulant(s) sufficient to enhance alertness, memory and wakefulness during the day, while minimizing the side effects that result from such a treatment..." The Examiner concludes that "given what was known independently about pharmaceuticals composed primarily of d-isomer and those composed primarily of l-isomer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine both d-isomer and l-isomer in such a way as to enhance wakefulness and memory during the day but to minimize the effects that such stimulants have on disturbing sleep patterns."

The Examiner states that one of ordinary skill in the art "would have been motivated to [produce the claimed invention] in order to maintain alertness, wakefulness, attention and enhanced memory function for the entire, or almost the entire, day but to minimize the disruptive effect of stimulant therapy on sleep patterns ..."

Further, citing Remington, the Examiner contends that "it would have been well within the purview of the skilled artisan to employ such a combination therapy ... as one single dosage form or two separate dosage forms such that more d-isomer than l-isomer was released immediately following administration and the release of l-isomer was delayed such that the latter portion of the therapeutic effect was attributable to a greater release of l-isomer than d-isomer."

The Examiner also contends that "it would have been a matter well within the purview of one of ordinary skill" to determine the optimum molar ratios.

The Applicant respectfully traverses these rejections. The Examiner presumes that stating the problem (finding an acceptable balance of effectiveness and side effects) leads *ipso facto* to its solution. However, no teaching is provided of how to combine the teachings to solve this problem, or to do so in the way the inventors did here. An invitation to experiment is not obviousness.

The suggestion or motivation to combine must come from the references themselves. Here, a *prima facie* case of obviousness has not been made out because no such suggestion or motivation has been provided. The references do not provide the motivation or suggestion to

produce a pharmaceutical composition wherein the molar ratio of l-amphetamine to d-amphetamine released is greater later in the day. See, *In re Gorman*, 933 F.2d 982 (Fed. Cir. 1991) ("The references themselves must provide some teaching whereby the applicant's combination would have been obvious.").

Applicant respectfully notes that the Examiner has impermissibly used hindsight to reconstruct the invention by picking and choosing among the several different references. See *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991) ("We do not 'pick and choose among the individual elements of assorted prior art references to recreate the claimed invention,' but rather, we look for 'some teaching or suggestion in the references to support their use in the particular claimed combination.'").

*The primary reference:*

Patrick discloses that ADDERALL® is the only amphetamine formulation that contains levoamphetamine (a "minor component") (Patrick at 537). However, Patrick includes only one suggestion as to why levoamphetamine would be included in an amphetamine formulation<sup>1</sup>, and expressly states that the therapeutic significance for including levoamphetamine is unknown. Patrick does not come close to suggesting that a predominance of levoamphetamine release later in the day is desirable. In fact, Patrick questions why levoamphetamine is included at all. For example, according to Patrick:

- "[T]he rationale for inclusion of the levo isomer remains unclear" (Patrick at 527, abstract).
- "Side effects associated with levoamphetamine component of this mixture, as with dextroamphetamine, are generally sympathomimetic in nature" (Patrick at 538). Thus, Patrick does not recognize that levoamphetamine has a different/more desirable side effect profile than dextroamphetamine. Accordingly, no motivation is provided to manipulate the molar ratio of the isomers.

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<sup>1</sup> "A rationale for the inclusion of both dextroamphetamine and levoamphetamine based on preferential influences on dopamine versus norepinephrine systems, respectively, has been suggested" (Patrick at 538).

- “Racemic amphetamine (dextroamphetamine and levoamphetamine, 50:50) was the first psychostimulant used to treat children with behavioural disorders (Bradley, 1937) .... [Because] dextroamphetamine is more frequently the most efficacious ... levoamphetamine is not a marketed drug product in its own right” (Patrick at 536). Patrick does not recommend or suggest reintroduction of levoamphetamine into the market.

- “Adderall® ... is the only amphetamine formulation containing levoamphetamine (but as a minor component) .... Such a mixture of different salts may possibly influence the dissolution rates, modifying the absorption characteristics relative to dextroamphetamine sulfate. However, there are no published studies assessing Adderall® pharmacokinetics, nor pharmacodynamics, safety or efficacy in ADHD” (Patrick at 537-38).

- “The therapeutic significance of the mixed salts of amphetamine has yet to be established” (Patrick at 539, conclusion).

As explained above, Patrick does not even remotely motivate one of ordinary skill in the art to produce an amphetamine formulation with the claimed molar ratio and release characteristics.

*The secondary references:*

1. Hartman does not disclose or suggest administering a combination of d- and l-amphetamine, much less d- and l- amphetamine in specified ratios wherein the ratio changes as the day progresses. See Hartman at 172 (“Each subject took ... placebo, d-amphetamine sulfate 10 mg, or l-amphetamine sulfate 10 mg ...”).

2. Epstein discloses the use of an amphetamine composition enriched in one enantiomer. However, Epstein does not disclose or suggest a formulation wherein the ratio of l-amphetamine relative to d-amphetamine is greater later in the day.

3. The Drug Facts and Comparisons publication relates to both racemic amphetamine sulfate and dextroamphetamine sulfate products (Drug Facts and Comparisons, page 1233). All statements in this publication are directed to amphetamines generally. There is no mention of any differences between d- and l- amphetamine. Contrary to the Examiner, the reference does not teach

